NEWS

New approach may treat autism by dialing up genes

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Injecting snippets of RNA into the brain could gently boost the expression of certain genes, according to a mouse study[1]. The finding could help safely treat some forms of autism.

Many mutations associated with autism affect only one copy of a gene, leaving the other intact. In these cases, researchers could use RNA snippets to boost the expression of the undamaged copy.

In the new work, described 20 December in *Scientific Reports*, researchers increased the expression of the **FOXG1** gene in mice. Missing one copy of FOXG1 leads a developmental condition that **resembles Rett syndrome**, which is characterized by motor deficits, language delay and autism features. Too much FOXG1, on the other hand, could lead to a form of **epilepsy** called West syndrome.

When the researchers injected RNA fragments specific to FOXG1, the gene's activity rose only slightly, minimizing the chances of side effects from a potential overdose.

"You don't get a spectacular result, but just a gentle over-activation of the gene," says lead researcher **Antonello Mallamaci**, associate professor of molecular biology at SISSA in Trieste, Italy.

The method also does not appear to boost the gene in cells that don't normally express it. "You will never activate the silent gene," Mallamaci says. "This is extremely important."

Recruitment strategy:

It is still unclear how the snippets, called RNAa molecules, ramp up gene expression. Because of this, the researchers can't rule out the possibility that it spur unwanted expression elsewhere in the

genome, says **Stormy Chamberlain**, assistant professor of genetics and genome sciences at the University of Connecticut in Farmington, who was not involved with the study.

What's more, not all mutations inactivate a gene, says **Michael Wigler**, professor at Cold Spring Harbor Laboratory in New York, who was not involved in the study. In some cases, a mutation can lead to an abnormal protein that is toxic to the cell. Determining a mutation's exact effect would be essential before applying the new technique, Wigler says. "With the caveat that you know your mutation is debilitating, this is a very exciting approach," he says.

Mallamaci and his colleagues engineered RNAa molecules that bind to the regulatory regions of DNA near FOXG1. These molecules enhance gene expression, possibly by loosening the gene's tightly coiled DNA and allowing the cell's regulatory machinery to access it.

Alternatively, the molecules may directly recruit the regulatory molecules to a gene. The researchers have preliminary evidence for this second possibility.

Fine-tuning:

The researchers tested eight RNAa molecules in neuronal stem cells from embryonic mice. Each of the molecules increases FOXG1 expression in the cells. One of them also enhances FOXG1 expression in mature mouse neurons, which puts researchers a step closer to treating the genetic condition in people.

Using a virus, the researchers delivered the RNAa that works in mature neurons to the brains of newborn mice. Three weeks later, FOXG1 expression was 66 percent higher overall in the brains of the treated mice than in those of controls.

The method may need tweaking, however, because expression in the subset of neurons that respond to the treatment may be too high, Mallamaci says.

FOXG1 expression typically increases in response to the elevated levels of potassium that accompany neural activity. The researchers found that adding potassium to RNAa-treated cells further enhances FOXG1 expression. This result indicates that expression in response to RNAa still hews to normal ebb and flow of expression in the cell.

"It is very promising to me that this approach respects the endogenous fine-tuning of the gene," says Mallamaci.

Mallamaci and his team plan to look at the effect of boosting FOXG1 expression in mice that lack one copy of the gene.

REFERENCES:

1. Fimiani C. *et al. Sci. Rep.* **6**, 39311 (2016) **PubMed**