NEWS

Snippets of RNA may reverse symptoms of Angelman syndrome

BY **JESSICA WRIGHT**

4 DECEMBER 2014

Lost and found: Small bits of RNA activate a normally silent copy of UBE3A attached to a fluorescent protein.

Small pieces of RNA restore the expression of a key gene missing in **Angelman syndrome** and offer the promise of a highly specific cure, researchers reported Monday in *Nature*[1].

Injecting these RNA snippets into the brains of mice missing one copy of this gene, called UBE3A, reverses their memory problems.

“If you would have asked me 15 years ago when we were first finding this gene if I thought that a cure ever would have been a possibility, I would have said it was a slim chance,” says lead researcher **Arthur Beaudet**, professor of molecular and human genetics at Baylor College of Medicine in Houston, Texas. “Now there’s room to be much more optimistic than that.”

The copy of UBE3A inherited from the father is typically always silent. Because of this, mutations that hobble the maternal copy result in Angelman syndrome, a disorder characterized by developmental delay, seizures, poor muscle coordination and autism symptoms. Researchers have investigated restoring the intact paternal copy’s expression as one way to treat the syndrome.

A 2011 study found that topotecan, a cancer drug, **restores UBE3A expression** in mice lacking

the maternal copy of the gene[2]. But the drug also affects the expression of other genes, and may lead to side effects common in chemotherapy, such as hair loss, nausea and anemia.

The new method instead uses RNA sequences that are specific to UBE3A.

“What’s wonderful about this is that it provides the opportunity to have really great specificity,” says **Benjamin Philpot**, professor of neuroscience at the University of North Carolina at Chapel Hill, who led the topotecan study but is not involved in the new work.

Silencing stop:

The new approach is possible because of the unusual way in which the paternal UBE3A gene is silenced. An ‘antisense’ RNA normally blocks protein production from the paternal copy of UBE3A[3].

Last year, Beaudet’s team found that engineering neurons so that they don’t make this antisense RNA molecule restores the expression of paternal UBE3A[4]. In the new study, the team screened nearly 250 snippets of RNA and found 2 that bind the antisense molecules. An enzyme destroys the resulting double-stranded RNA, effectively unlocking UBE3A expression.

In cultured mouse neurons, adding the RNA snippets restores UBE3A expression to about 90 percent of its normal levels. Injecting them into adult mouse brains is less effective, bringing it up to 47 percent of normal levels, depending on the brain region. This effect persists up to four months after the injection.

In people with Angelman syndrome, the treatment would require repeated injections into the spinal fluid because the RNA pieces cannot cross the blood-brain barrier. This may cause damage to the spine over time.

A drug like topotecan that **has more long-lasting effects** on UBE3A expression may be preferable, says Philpot. Some topotecan crosses into the brain, but Philpot is looking for compounds with a similar mechanism, better brain delivery and fewer side effects.

“I would happily lose the race to get a treatment for Angelman syndrome,” he says. “But I think it’s probably premature to give up on one or the other approach. They really offer different advantages and disadvantages.”

Any attempts to reverse Angelman syndrome are likely to work best if introduced early in life.

In unpublished work presented in August at a joint scientific symposium presented by the Dup15q Alliance and the Angelman Syndrome Foundation in Boston, **Ype Elgersma** showed that restoring UBE3A expression **reverses motor deficits in 3-week old mice**, but not their 14-week-old

seniors. This suggests there is a critical window for curing the disorder.

In the new study, the researchers only treated adult mice. The treated adults are no longer obese and perform better on a task of learning and memory, but still show motor deficits and anxiety.

“The results could be even better if it were done in young animals, if we are going to treat young children rather than adults,” says Elgersma, professor of neuroscience at Erasmus University in Rotterdam, the Netherlands, who was not involved in the new study.

Beaudet says it might be possible to treat Angelman syndrome starting at birth by screening all newborns for the disorder. But researchers will first need to ensure that the RNA is just as safe and specific in people as it appears to be in mice.

“It’s promising, but I don’t think they’ll be able to go straight from these sequences in mice and translate into humans,” says **Jeanine LaSalle**, professor of medical microbiology and immunology at the University of California, Davis.

In the meantime, ISIS pharmaceuticals, the company that makes the RNA fragments, has shown in a small trial that injecting RNA into spinal fluid to treat spinal muscular atrophy is safe. “It’s very good precedent for feasibility of delivery to children,” says Beaudet.

References:

1: Meng L. *et al. Nature* Epub ahead of print (2014) **Abstract**

2: Huang *et al. Nature* **481**, 185-189 (2011) **PubMed**

3: Meng L. *et al. Hum. Mol. Genet.* **21**, 3001-3012 (2012) **PubMed**

4: Meng L. *et al. PLoS Genet.* **9**, e1004039 (2013) **PubMed**