NATURE | NEWS

A wake-up call for dormant genes

Anti-cancer drug holds potential as a treatment for genetic-imprinting disorder.

Rebecca Hill

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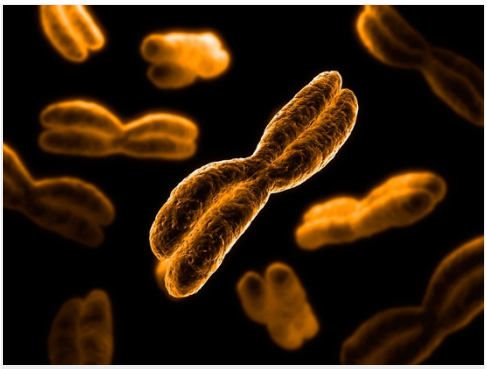
The silenced copy of a gene could be reactivated to treat the neurodevelopmental disorder Angelman syndrome. A study published today in *Nature*[1] reveals that a common anti-cancer drug can turn on the normally dormant paternal *Ube3a* allele in the brains of mice.

Angelman syndrome, first described in 1965[2], is characterized by jerky movements, seizures, learning disabilities and frequent laughter. It affects around 1 in 15,000 newborn children.

The *UBE3A* gene codes for the protein UBE3A, which regulates degradation of unnecessary proteins and is involved in nervous-system development. Everyone inherits one copy of the gene, called an allele, from each parent, but only the maternal version is expressed in neurons; the paternal copy is switched off in a process known as imprinting. In 70% of people with Angelman syndrome, the maternal *Ube3a* allele is mutated or deleted. This means that the UBE3A protein is not produced.



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Some sections of chromosome normally remain dormant; drugs that reactivate them could help to treat Angelman syndrome and other disorders.

Benjamin Philpot and Mark Zylka, cell biologists at the University of North Carolina School of Medicine in Chapel Hill, led a research team that reasoned that if the paternal allele could be turned back on, functional UBE3A would be made in the neurons.

“You’ve got a perfectly good allele sitting there, not being used,” explains Paul Greer, a neurobiologist at Harvard Medical School in Boston, Massachusetts. “Turning it back on is a phenomenal idea.”

Unexpected answer

After screening around 2,300 compounds for one that could reactivate the gene, Philpot and Zylka's team lighted on a group of anti-cancer drugs known as topoisomerase I inhibitors.

That was something of a surprise, because it is a completely new application for the drugs. “It is utterly remarkable that of all the compounds out there, topoisomerase inhibitors do the trick. We would have never thought of that in a million years,” says Zylka.

Topoisomerases are proteins that bind to DNA during replication to help copy the chromosome. Topoisomerase inhibitors make this binding permanent, eventually breaking the DNA. So how are they unsilencing paternal *Ube3a*? “We spent a lot of time asking this very question,” says Zylka. The team isn't sure of the exact mechanism yet, but Zylka says that the drugs seem to turn down the expression of the antisense genetic transcript *Ube3a-ATS*, which normally blocks paternal *Ube3a* expression[3].

Next, the group looked at levels of *Ube3a* expression in the neurons of mice injected with one of these drugs, topotecan. Not only was the paternal allele unsilenced, but the effects continued for up to 12 weeks after treatment. Philpot is hopeful that the change will prove to be permanent, but notes that it might be different in other types of cells.

Trial period

At present, people with Angelman syndrome can receive treatment only for their symptoms, not for the underlying condition. “This research could open up a lot of possibilities for Angelman syndrome and, in principle, for the treatment of other neurogenetic disorders,” says Bernard Dan, a neuropaediatrician at the Free University of Brussels, who has studied the condition for 15 years.

But, says Dan, medicine is “still very far from a cure — even if you restore gene expression, it’s at a relatively late stage in the brain’s maturation; we don’t know if it will rewire the brain completely”.

The authors caution that although some topoisomerase inhibitors have been approved for treatment of cancer in many countries, they are not yet close to being used to treat Angelman syndrome. Mice can tolerate higher doses of the compounds than humans[4], and researchers don't yet know how much will be needed for effective treatment. "The really pressing concern is that people will start using off label," explains Philpot. "Not only is it a risk to the individual, it could jeopardize future clinical trials."

The team has funding for pre-clinical trials of topoisomerase inhibitors. Philpot says, "Now we've figured out the difficult process of analysing treatments in primary neurons, we're eager to apply it to other disorders."

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References

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