NEWS

Molecular mechanisms: Study shows Angelman drug's actions

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Site specificity: A cancer drug activates both copies of UBE3A (left, arrows), but not in cells lacking a certain genetic region (right).

Researchers have uncovered the mechanism by which a candidate drug for **Angelman syndrome** activates **UBE3A**, the gene that is silenced in the syndrome, according to a study published 20 August in the *Proceedings of the National Academy of Sciences*[1].

This may allow scientists to develop drugs that specifically target UBE3A, the researchers say.

Angelman syndrome is an autism-related disorder **characterized by developmental delay**, seizures, lack of speech and an unusually happy demeanor. The disorder is the result of mutations in or deletions of the maternal copy of UBE3A.

Neurons typically express only the maternal copy of UBE3A, so the mutations result in a complete lack of the protein in the brain.

In a 2011 study, researchers reported that **a cancer drug called topotecan** activates the paternal copy of UBE3A in neurons, and could be used to treat Angelman syndrome. The drug is known to inhibit topoisomerases, **an important family of enzymes that untangle DNA**.

Preliminary results suggested that topotecan unsilences only UBE3A and not other genes, but the

reason for this specificity was unclear.

In the new study, researchers homed in on how topotecan affects UBE3A expression. In brain cells, the paternal copy of UBE3A is silenced by a piece of RNA, called UBE3A-antisense.

The stretch of DNA that encodes UBE3A-antisense is located next to gene called SNORD116. Topotecan lowers the production of UBE3A-antisense, which then unsilences UBE3A. However, topotecan has no effect in cells lacking SNORD116, suggesting that it functions at the SNORD116 site.

Because of its sequence, SNORD116 is especially prone to R-loops, genetic structures that form between RNA and DNA. Topotecan increases the number of these loops, which prevents UBE3A-antisense from forming, and so allows UBE3A expression.

Drugs that increase the number of R-loops in SNORD116 may offer a more specific way to treat Angelman syndrome than inhibiting topoisomerases, the researchers suggest.

References:

1: Powell W.T. *et al. Proc. Natl. Acad. Sci. USA* **110**, 13938-13943 (2013) **PubMed**