How a cancer drug unties knots in the chromosome that causes Angelman and Prader-Willi syndromes

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UC Davis researchers have identified how and where in the genome a cancer chemotherapy agent acts on and 'un-silences' the epigenetically silenced gene that causes Angelman syndrome, a rare neurodevelopmental disorder characterized by severe intellectual disability, seizures, motor impairments, and laughing and smiling.

The agent, Topotecan, is a topoisomerase inhibitor, part of a class of drugs that in earlier research has been found to un-silence the Angelman gene, suggesting that it might be therapeutic for the condition, which affects approximately 1 in 25,000, or approximately 150,000 people worldwide. But how it acts has not been known.

Topotecan is primarily used to treat metastatic cancers, including ovarian cancer, cervical cancer and small-cell lung cancer, by preventing cells from dividing and causing their death.

The research, published online today in *Proceedings of the National Academy of Sciences* (PNAS), found that the drug stabilizes the formation of strands of RNA that create RNA-DNA hybrids called 'R-loops,' in the Ube3a region of the gene15q11-q13. The gene is implicated in other neurodevelopmental disorders, including autism. About 1 percent of cases of autism are linked to duplications in 15q11-q13 or "Dup15q," children that over-express Ube3a.

"Now we have a molecular mechanism for a proposed drug for a disease, so we can understand how it works and begin to tweak it to develop therapies," said lead study author Weston Powell, a third-year medical student in the Physician Scientist Training Program in the UC Davis School of Medicine.

Angelman syndrome is caused by the loss of a maternally inherited Ube3a gene at the 15q11-q13 locus, which is expressed in brain neurons. Loss of the same chromosomal region inherited from the male parent causes another neurodevelopmental condition, Prader-Willi syndrome, best known for its sufferers' obsessive-compulsive behavior and insatiable appetites which, if left unchecked, can lead to morbid obesity.

DNA is like a twisted rope, Powell explained, which opens as the enzyme polymerase travels down one thread of the rope to produce an RNA copy of the DNA strand. Normally the RNA leaves the DNA, but sometimes the RNA instead sticks to one piece of DNA, and an 'R-loop' is formed. These hybridized DNA-RNA loops create tension, preventing the DNA from having the characteristic flexibility that allows it to form its spiral helix or twisted-rope shape. R-loops themselves are a relatively recent discovery, and researchers have just begun to understand how they function.

While the discovery of the effect of Topotecan is important, future investigations will determine how and whether the drug may have therapeutic applications for Angelman syndrome, the researchers said.

"Topotecan also has an effect everywhere in the genome," Powell said. "One of the things it does is prevent cells from dividing. That's why it's a cancer drug. But that's also a problem if you want to treat children, because it kills dividing cells."

Powell said that additional investigations are needed to determine whether the drug can be tweaked to eliminate the global effect and only treat the targeted region.

Senior study author Janine LaSalle, professor of

microbiology and immunology and a researcher affiliated with the UC Davis MIND Institute, said that the study highlights the significance of epigenetics in understanding both rare and more common neurodevelopmental disorders.

"What determines whether you have Prader-Willi syndrome or Angelman syndrome is whether the maternal or paternal gene is missing," LaSalle said. "These are the classic, textbook epigenetic disorders involving parental imprinting. It's not just about the chromosomes, but it's where—or who—they come from. In our study, we show that R-loops forming on the active paternal chromosome within the Prader-Willi region regulate imprinting of the Angelman gene, Ube3a, on the maternal chromosome.

"Epigenetics is the layers that are put on top of the genetic code by the environment. In the case of the imprinted inheritance of these two diseases, it's simply the environment of whether the chromosomes travel through the egg or the sperm. But environmental influences, such as diet and exposure to pollutants, also affect the epigenetic layers and are becoming increasingly important in more common disorders such as autism."

LaSalle said that the finding also is important because the diseases are caused by defects in a common chromosomal locus for autism-spectrum disorders. Rearrangements in 15q are increasing, she said, in both non-human primates and people. Her lab has recently found an association between polychlorinated biphenyl (PCB) levels and 15q rearrangements in human postmortem brain. Future investigations will examine the role of current persistent organic pollutants, such as polybrominated diphenyl ethers (PBDEs), that may have a role in promoting chromosomal rearrangements and epigenetic alterations in this region.

More information:
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