

Study shows epigenetic changes can drive cancer

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Cancer has long been thought to be primarily a genetic disease, but in recent decades scientists have come to believe that epigenetic changes – which don't change the DNA sequence but how it is 'read' – also play a role in cancer. In particular DNA methylation, the addition of a methyl group (or molecule), is an epigenetic switch that can stably turn off genes, suggesting the potential to cause cancer just as a genetic mutation can. Until now, however, direct evidence that DNA methylation drives cancer formation was lacking.

Researchers at the USDA/ARS Children's Nutrition Research Center at Baylor College of Medicine and Texas Children's Hospital have now created a mouse model providing the first in vivo evidence that epigenetic alterations alone can cause [cancer](#). Their report appears today in the *Journal of Clinical Investigation*.

"We knew that epigenetic changes are associated with cancer, but didn't know whether these were a cause or consequence of cancer. Developing this new approach for 'epigenetic engineering' allowed us to test whether DNA methylation changes alone can drive cancer," said Dr. Lanlan Shen, associate professor of pediatrics at Baylor and senior author of the study.

Shen and colleagues focused on p16, a gene that normally functions to prevent cancer but is commonly methylated in a broad spectrum of human cancers. They devised an approach to engineer DNA methylation specifically to the mouse p16 regulatory region (promoter). As intended,

the engineered p16 promoter acted as a 'methylation magnet'. As the mice reached adulthood, gradually increasing p16 methylation led to a higher incidence of spontaneous cancers, and reduced survival.

"This is not only the first in vivo evidence that epigenetic alteration alone can cause cancer," said Shen. "This also has profound implications for future studies, because epigenetic changes are potentially reversible. Our findings therefore both provide hope for new epigenetic therapies and validate a novel approach for testing them."

Shen, who is also with the NCI-designated Dan L. Duncan Cancer Center at Baylor, predicts that this new approach will be widely useful because in addition to p16, there are many other genes and diseases other than cancer that are connected to epigenetics (such as neurodevelopmental diseases, obesity and diabetes). Just as genetic engineering has become a standard approach for studying how genetic mutations cause disease, epigenetic engineering will now enable functional studies of epigenetics.

"This opens up the door for a whole new paradigm of how to understand tumorigenesis. If we can identify [epigenetic changes](#) that predispose people to cancer, these may actually be treatable or preventable, so this opens up a lot of optimism in new ways to deal with cancer," said Dr. Robert Waterland, associate professor of pediatrics at Baylor, who was also involved in the study.

Provided by Baylor College of Medicine

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