

Mechanism behind demethylation pinpointed in APC gene mutants

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Researchers at Huntsman Cancer Institute at the University of Utah demonstrate in a study featured in *Cell* the mechanism by which mutation of the APC gene affects a cellular process known as DNA methylation.

Colon cancer is the second most common cancer in the United States and causes more than 50,000 deaths each year. It has been known for some time that [mutations](#) in the APC gene occur in more than 85 percent of all sporadic colon cancers. Now researchers at Huntsman Cancer Institute at the University of Utah demonstrate in a study featured today in *Cell* the mechanism by which mutation of the APC gene affects a cellular process known as DNA methylation. DNA methylation is a chemical modification made to DNA that plays an important role in dictating how DNA is read and interpreted by a cell.

The group, led by David Jones, Ph.D., and Bradley Cairns, Ph.D., have now linked loss of Apc with DNA demethylase, an enzyme system that erases DNA methylation. Studies using human tissues and zebrafish demonstrate that this system is highly active in tissues harboring mutated Apc and may provide an explanation for the previously known loss of [DNA methylation](#) seen in early stage tumors. The activity of the DNA demethylase appears to stall the normal development of [intestinal cells](#), leaving them in a stem cell-like state. Normal development was restored upon [inhibition](#) of the DNA demethylase system. The experiments conducted by the group also demonstrated that the mechanistic connection between APC mutation and demethylation is conveyed

through changes in the amount of retinoic acid (RA), an important regulatory compound derived from dietary vitamin A.

"We believe that clarification of the mechanism leading to demethylation will have broad implications for a variety of cancers. Our increased understanding of the mechanics connecting APC mutation and demethylation presents new opportunities for [colon cancer](#) intervention and may lead the way to developing a truly finely tuned approach to treatment," said Jones. Cairns added, "Since the mechanism of action of the demethylase can inherently create new mutations, misregulation of the system could underlie the occurrence of mutations in additional oncogenes. Its inhibition may therefore allow us to both prevent and treat certain cancers."

Provided by University of Utah

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