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DNA enhancers switch on colorectal cancer genes to promote tumor growth, study finds

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Genetic mutations can increase a person's cancer risk, but other gene "enhancer" elements may also be responsible for disease progression, according to new research out of Case Western Reserve University School of Medicine. In a breakthrough study published in *Nature Communications*, scientists discovered changes in specific regions of DNA, outside of colorectal cancer genes, that "enhance" harmful gene expression to help grow tumors. The changes are highly conserved across tumor samples, suggesting a common mechanism that could be targeted by drug developers.

Enhancer elements are short sections of DNA that function as switches to control genes. They are sprinkled throughout the genome, interfacing with distant genes as DNA twists and folds into complex 3-D structures. The new study found that the chromosomes of colorectal cancer genes harbor "hotspots" of high enhancer activity that switch on, or activate, genes.

"Our data suggest that the survival of colon cancer cells often depends on the expression of genes associated with common enhancer changes," said Peter Scacheri, PhD, senior author on the study and associate professor of genetics and genome sciences at Case Western Reserve University School of Medicine. According to Scacheri, the common enhancer changes also align with specific DNA sequences known to increase one's lifetime risk of developing colorectal cancer.

Scacheri's team identified thousands of enhancer elements unexpectedly altered across colorectal cancer samples. When the researchers genetically manipulated the enhancer elements, colorectal cancer genes previously activated were deactivated. The researchers propose that manipulating enhancer elements could be one way to turn off colorectal cancer genes and slow tumor progression.

The study tested 42 genetically diverse colorectal cancer samples, "representing the most extensive delineation of enhancer alterations in a single type of cancer to date," according to the paper. The study acknowledges previously identified genetic mutations that lead to colorectal

cancer, but indicates DNA regions outside of cancer genes also play a role in disease. The researchers suggest enhancer elements and mutations work in tandem to cause colorectal tumors.

"Enhancer elements are distinguishable by specific chemical tags on DNA, like bulbs on a string of lights," said Scacheri. "Identifying common enhancer changes helps us pinpoint a specific set of genes that are consistently switched on during transformation of normal cells to cancer cells. These genes define the tumor state, and therefore could be just as important to tumor growth as those that are commonly mutated."

Colorectal cancer causes fatal tumors in men and women and is the second leading cause of cancer-related death in the United States, according to the Centers for Disease Control and Prevention. Recurrent changes in enhancer elements could serve as new therapeutic targets to fight the disease. Said Scacheri, "Our next step is to determine exactly how the common enhancers form in colon cancer, and whether we can target their destruction as a strategy to kill tumor cells without harming normal cells."

Source:

http://casemed.case.edu/newscenter/news-release/newsrelease.cfm?news_id=523
