

Scientists discover a genetic mechanism for cancer progression

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Cancer—Histopathologic image of colonic carcinoid. Credit: Wikipedia/CC BY-SA 3.0

Genetics researchers from Case Western Reserve School of Medicine have identified a novel long non-coding RNA (lncRNA), dubbed DACOR1, that has the potential to stymie the growth of tumor cells in the second-most deadly form of cancer in the U.S.—colorectal cancer.

The researchers found that this lncRNA is present in cells of healthy colons, but becomes suppressed in those carrying the disease. More importantly, this lncRNA interacts with a key enzyme known as DNMT1 that has important functions in all healthy cells of the body. Thus, the authors applied a name to this novel lncRNA—DACOR1, which stands for DNMT1-Associated Colon Cancer Repressed lncRNA-1.

The scientists' next challenge is to determine how to deliver DACOR1 to tumors where it may be able to slow, or even stop, the spread of malignant cells. The researchers' initial findings appeared in this month's edition of *Human Molecular Genetics*.

"We found that the metabolism of [cancer](#) cells slows when we put DACOR1 back in," said senior author Ahmad M. Khalil, PhD, an assistant professor of genetics and genome sciences. "If we could figure out a way to deliver DACOR1 to tumors, we could change the methylation patterns in cancer cells to either destroy or at least regress tumors."

DNA methylation affects the molecule's function, including gene expression. Whenever a biological process affects genetic expression, the potential exists to promote health or cause disease. To understand what factors decide which outcomes in humans, scientists first identify how different molecules are supposed to act—and, in turn, the elements that make their functions go awry.

Khalil, a member of the Case Comprehensive Cancer Center, began the journey to the team's discovery with a hypothesis—namely, that lncRNA molecules directly regulate the enzyme DNMT1 that adds methylation to DNA. This ongoing chemical modification of our DNA—a process known as DNA methylation—can help prevent cancer by maintaining a healthy level of gene expression, which in turn controls the extent of cell growth in the body.

During their research, investigators found that specific lncRNAs regulate DNA methylation in specific human genes. Researchers also sought clues on how lncRNAs affect normal tissue versus cancerous tissue and characterized one particular lncRNA, DACOR1, which is present in healthy colon tissue but missing from colon cancer tissue.

"Cancer cells do not want certain lncRNAs around because they instruct normal cells to grow at a specific rate," said Khalil, the study's senior author. "Our research, in part, explains how cancer cells change their DNA methylation pattern, and this change is a major mechanism where normal cells become cancer cells."

Methylation is a process where a methyl group is added into critical points along our DNA. In cancer, many regions of the DNA are not methylated, leading to untimely gene expression, and unwanted cell reproduction. In some instances, genes that trigger cancer, known as oncogenes, spring into action.

DNA methylation occurs through enzymes known as DNA methyltransferases (DNMTs), and there are only three of them in the human genome: DNMT1, DNMT3A and DNMT3B. DNMT1 is the most important one because of its activity in all cell types, so investigators focused on how a subset of lncRNAs might interact with DNMT1. Khalil's hypothesis was that a subset of lncRNAs interacts with DNMT1 and that cancer cells alter the expression of these specific lncRNAs to change the location of where the DNMT1 enzyme triggers methylation along the DNA.

In their research, Khalil's team first isolated 148 lncRNAs from 8,300 known lncRNAs. These 148 lncRNAs are associated with DNMT1 in [colon cells](#). To test their hypothesis in depth, the researchers focused their study on a key lncRNA that becomes suppressed in colon cancer—DACOR1.

Then investigators obtained normal and cancerous colon tissue from public datasets and compared how DACOR1 acted within each. They found that DACOR1 is active in normal colon tissue but repressed in colon cancer tissue. Similar results were found in studying 21 colon cancer cell lines from the Markowitz Laboratory of Genetic Colon Cancer Research at Case Western Reserve—DACOR1 is suppressed in colon cancer.

Investigators also pondered whether returning DACOR1, and therefore, DNA methylation, to [colon cancer cells](#) would slow their growth. The answer was yes. In two colon cancer cell lines, the DNA methylation pattern changed when the lncRNA DACOR1 was injected into the cells. Additionally, investigators placed DACOR1 into cancer cells to track where this specific lncRNA went. DACOR1 returned to those cancer-suppressing regions of the DNA where it had been missing in the cancer cells.

"These experiments showed us that DNMT1-associated lncRNAs are regulating DNA methylation and subsequent gene expression, which controls cell growth," Khalil said.

Next steps for Khalil's team will be more research into DACOR1 and the effects of other lncRNAs believed to suppress colon cancer. Perhaps defects in a number of lncRNAs work in synergistic unison to drive the onset of colon cancer. Eventually, the potential is there to develop a therapy that would reactivate key lncRNAs in their job of maintaining normal, controlled cell growth and prevent unbridled [cell growth](#) leading to cancer. If nothing else, the lack of colon cancer-repressing genes could serve as an early-detection biomarker for [colon cancer](#).

"Clearly, [cancer cells](#) have a way of changing [gene expression](#) in a way that is advantageous to them, but how they do that, we don't entirely understand yet," Khalil said. "We do know now that cancer changes the

expression of key cancer-suppressing lncRNAs in a way that is advantageous to cancer cell proliferation."

Provided by Case Western Reserve University

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