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Researchers identify cancer-causing gene in many colon cancers

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Demonstrating that despite the large number of cancer-causing genes already identified, many more remain to be found, scientists at Dana-Farber Cancer Institute have linked a previously unsuspected gene, CDK8, to colon cancer.

The discovery of CDK8's role in cancer was made possible by new tools for assessing the activity of specific genes, say the authors of the new study. As these tools are further improved, the stream of newly discovered cancer genes is expected to increase, providing new avenues for therapy, the authors suggest. The findings are being published as an advanced online publication by the journal *Nature* on Sept. 14.

"This study provides confirmation that many of the genes involved in cancer have yet to be identified," remarked the study's senior author, William Hahn, MD, PhD, of Dana-Farber and the Broad Institute of Harvard and M.I.T. "When it comes to identifying gene targets for therapy, we've really only scratched the surface."

The study is noteworthy in another respect, as well, the authors indicated. Many of the abnormal proteins linked to cancer are known as "transcription factors" because they're able to "read" cell DNA and use that information for producing other cell proteins. Although transcription factors are important regulators, this class of proteins has proven to be impossible to target with drugs. Genes that influence such transcription factors, however, make attractive targets for drugs, since they can potentially disrupt the cancer process and disable tumor cells.

CDK8 is such a gene.

The new study began with a focus on a protein called beta-catenin, a transcription factor that is overactive in nearly all colorectal cancers. Although overactive beta-catenin plays a role in the initial formation of tumors, other genetic abnormalities must occur for tumors to become fully malignant.

To determine which genes control the production of beta-catenin and are involved in the proliferation of colon cancer cells, the research team ran three screening tests. In the first two, they used RNA interference to shut down more than a thousand genes one by one and recorded the instances where beta-catenin activity decreased and the cells stopped growing. They then analyzed colon cancers for genes that had extra copies. When they examined where the results of the three tests overlapped, one gene stood out -- CDK8, explained Hahn, who is also an associate professor of medicine at Harvard Medical School

The protein produced from CDK8 is part of the "mediator complex," a conglomeration of proteins that serves as a bridge for compounds involved in gene transcription. "This study demonstrates that blocking CDK8 interferes with the proliferation of colon cancer cells that have high levels of the CDK8 protein and overactive beta-catenin," Hahn said. "Drugs that target CDK8 may be very useful against tumors whose growth is driven by beta-catenin."

Source: Dana-Farber Cancer Institute