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Turned-off Cannabinoid Receptor Turns on Colorectal Tumor Growth

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Contact Information

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Description

New preclinical research shows that cannabinoid cell surface receptor CB1 plays a tumor-suppressing role in human colorectal cancer, scientists report in the Aug. 1 edition of the journal *Cancer Research*.

Newswise — New preclinical research shows that cannabinoid cell surface receptor CB1 plays a tumor-suppressing role in human colorectal cancer, scientists report in the Aug. 1 edition of the journal *Cancer Research*.

CB1 is well-established for relieving pain and nausea, elevating mood and stimulating appetite by serving as a docking station for the cannabinoid group of signaling molecules. It now may serve as a new path for cancer prevention or treatment.

"We've found that CB1 expression is lost in most colorectal cancers, and when that happens a cancer-promoting protein is free to inhibit cell death," said senior author Raymond DuBois, M.D., Ph.D., provost and executive vice president of The University of Texas M. D. Anderson Cancer Center.

DuBois and collaborators from Vanderbilt-Ingram Cancer Center also show that CB1 expression can be restored with an existing drug, decitabine. They found that mice prone to developing intestinal tumors that also have functioning CB1 receptors develop fewer and smaller tumors when treated with a drug that mimics a cannabinoid receptor ligand. Ligands are molecules that function by binding to specific receptors. Agonists are synthetic molecules that mimic

Image Gallery



Raymond DuBois, M.D., Ph.D. Provost and Executive Vice President at M. D. Anderson Cancer Center.

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the action of a natural molecule.



Image 1 of 1



"Potential application of cannabinoids as anti-tumor drugs is an exciting prospect, because cannabinoid agonists are being evaluated now to treat the side-effects of chemotherapy and radiation therapy," DuBois said. "Turning CB1 back on and then treating with a cannabinoid agonist could provide a new approach to colorectal cancer treatment or prevention."

Cannabinoids are a group of ligands that serve a variety of cell-signaling roles. Some are produced by the body internally (endocannabinoids). External cannabinoids include manmade versions and those present in plants, most famously the active ingredient in marijuana (THC).

Receptor shutdown by methylation

Endocannabinoid signaling is important to the normal functioning of the digestive system and has been shown to protect the colon against inflammation. Since chronic inflammation is a known risk factor for colorectal cancer, the researchers decided to look into the role of cannabinoid receptors in a mouse model of colon cancer.

"People have looked at cannabinoids in cancer earlier, mainly in cell culture experiments," DuBois said. "The molecular mechanisms for loss of the receptor and its effect on cancer have not been previously shown."

First, the team found that CB1 was largely absent in 18 of 19 human tumor specimens and in 9 of 10 colorectal cancer cell lines. Further experimentation showed that the gene that encodes the CB1 protein was not damaged, but shut down chemically by the attachment of methyl groups - a carbon atom surrounded by three hydrogen atoms - to the gene encoding CB1.

Treating cell lines with decitabine, a demethylating agent approved for some types of leukemia, removed the methyl groups, restoring gene expression in 7 of 8 cell lines and full expression of CB1 protein in three lines.

Next, the group found that deletion of the CB1 gene in a strain of mice that spontaneously develops precancerous polyps resulted in a 2.5-to-3.8-fold increase in the number of polyps and a 10-fold increase in the number of large growths, those most likely to develop into cancer.

Treating mice that had the CB1 receptor with an endocannabinoid agonist resulted in a decline in polyps ranging from 16.7 percent to 50 percent. The reduction was greater for larger polyps.

CB1 thwarts survivin, a protein that protects cancer

Cannabinoids previously had been shown to kill cancer cells in lab experiments by inducing apoptosis - programmed cell death. The team confirmed the role of CB1 in apoptosis, showing that tumor cells with high CB1 expression were sensitive to apoptosis when treated by a cannabinoid agonist. Cell lines with silenced CB1 resisted cell death.

A series of experiments showed that CB1 increases cancer cell death by stifling a protein called survivin. Survivin is overexpressed in nearly every human tumor but is barely detectable in normal tissue, DuBois noted. Overexpression of survivin is associated with poor outcome and reduced apoptosis in colorectal cancer patients. The researchers pinpointed a cell signaling pathway by which activated CB1 cuts down survivin.

"Just increasing the levels of cannabinoids to treat colorectal cancer won't work if the CB1 receptor is not present," DuBois said. This suggests that treating first with a demethylating agent, such as decitabine, to reactivate CB1 in the tumor and following up with a cannabinoid might be an effective attack on colorectal cancer.

Scarcity of CB1 also is associated with Huntington's disease, Alzheimer's disease and multiple sclerosis. Further investigation, the researchers note, is needed to define its role in those diseases and other types of cancer. The team also analyzed the other main cannabinoid receptor, CB2, and found no role for it in colorectal cancer.

They also treated the mice with a CB1 antagonist, a compound that binds to the receptor but does not activate it. Mice with CB1 blocked in this manner also showed an increase in the number and size of polyps. A CB1 antagonist called rimonabant is currently marketed overseas for weight loss. The researchers note that a patient's risk for colorectal cancer should be assessed when use of such drugs is being considered.

The study was funded by grants from the National Cancer Institute and the National Colorectal Cancer Research Alliance.

Co-authors with DuBois are first author Dingzhi Wang, Ph.D., Haibin Wang, Ph.D., Wei Ning, Michael Backlund, Ph.D., and Dushansu K. Dey, Ph.D., all of the Vanderbilt-Ingram Cancer Center.

About M. D. Anderson

The University of Texas M. D. Anderson Cancer Center in Houston ranks as one of the world's most respected centers focused on cancer patient care, research, education and prevention. M. D. Anderson is one of only 39 Comprehensive Cancer Centers designated by the National Cancer Institute. For five of the past eight years, M. D. Anderson has ranked No. 1 in cancer care in "America's Best Hospitals," a survey published annually in U.S. News and World Report.

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