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Paired drugs kill precancerous colon polyps, spare normal tissue

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A two-drug combination destroys precancerous colon polyps with no effect on normal tissue, opening a new potential avenue for chemoprevention of colon cancer, a team of scientists at The University of Texas M. D. Anderson Cancer Center reports in the advance online edition of the journal *Nature*.

The regimen, tested so far in mouse models and on human colon cancer tissue in the lab, appears to address a problem with chemopreventive drugs - they must be taken continuously long term to be effective, exposing patients to possible side effects, said senior author Xiangwei Wu, Ph.D., associate professor in M. D. Anderson's Department of Head and Neck Surgery.

"This combination can be given short term and periodically to provide a long-term effect, which would be a new approach to chemoprevention," Wu said.

The team found that a combination of Vitamin A acetate (RAc) and TRAIL, short for tumor necrosis factor-related apoptosis-inducing ligand, kills precancerous polyps and inhibits tumor growth in mice that have deficiencies in a tumor-suppressor gene. That gene, adenomatous polyposis coli (APC) and its downstream signaling molecules, are mutated or deficient in 80 percent of all human colon cancers, Wu said.

Ineffective separately, powerful together

Early experiments with APC-deficient mice showed that the two drugs combined or separately did not harm normal colon epithelial cells. Separately, they showed no effect on premalignant polyps called adenomas.

RAc and TRAIL together killed adenoma cells, causing programmed cell suicide know as apoptosis. RAc, researchers found, sensitizes polyp cells to TRAIL.

The scientists painstakingly tracked the molecular cascade caused by APC deficiencies, and found that insufficient APC sensitizes cells to TRAIL and RAc by suppressing a protein that blocks TRAIL.

Reductions in polyps, improved survival

APC-deficient mice were treated with 15 cycles of the RAc/TRAIL combination over six weeks. Others received either RAc or TRAIL and a control group received nothing. One month later, control mice and those treated with one of the drugs averaged between 35 and 42 polyps, while those receiving the combination averaged 10.

To test the combination's potential as short-term therapy, APC-deficient mice were treated with two cycles of the combination in one week, causing a 69 percent polyp reduction two weeks later. A 10-fold increase in dose left treated mice with only 10 percent of the polyps found in controls.

A longer term test of relative survival using five treatments over four months improved survival from 186 days for controls to beyond 213 days for treated mice, with five of seven treated mice living more than eight months.

Cell death in human colon polyps

Next, the researchers treated biopsy samples of normal tissue and tumor regions from patients with familial adenomatous polyposis - an inherited condition that inevitably leads to colon cancer if the colon is not removed. Treatment of normal tissue caused little cell death, while 57 percent of polyp cells were killed via apoptosis.

Targeted therapies today aim at blocking some aspect of the tumor that drives its growth, Wu said, whereas RAc and TRAIL together kill precancerous polyps outright. Since APC is deficient or mutated in other types of cancer, the combination therapy could become a more general drug.

Before human clinical trials can be considered, Wu said, the team will conduct additional research to understand potential side effects and also will try to develop an injectable version of the combination, which is administered intravenously now.

One of the genes activated by the APC-deficient pathway, ß-catenin, is involved with stem cell self-renewal and maintenance in adult tissues. The team conducted a series of experiments and determined that RAc/TRAIL does not affect stem cells in mice.

Today, concerns about cardiovascular side effects limit chemopreventive agents for colon cancer mainly to high-risk patients, Wu said. "We hope this combination, if it proves to lack toxicities, might be available as a chemopreventive agent to a broader, general population."

Provided by University of Texas M. D. Anderson Cancer Center