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Vitamin D May Be Crucial in Preventing Colon Cancer

New studies by researchers at the Howard Hughes Medical Institute indicate that vitamin D protects against colon cancer by helping to detoxify cancer-triggering chemicals that are released during the digestion of high-fat foods.

The discovery, which was made by a team of researchers that included Howard Hughes Medical Institute (HHMI) investigators David J. Mangelsdorf at the University of Texas Southwestern Medical Center and Ronald M. Evans of The Salk Institute and colleagues at the University of Arizona, was reported in the May 17, 2002, issue of the journal *Science*.

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— David J. Mangelsdorf

The studies show that a specific type of bile acid, called lithocholic acid (LCA), which is a known carcinogen, activates the vitamin D receptor. When the vitamin D receptor is switched on, it triggers other proteins that detoxify the bile acid.

The research suggests that a drug that acts like vitamin D might help in preventing colon cancer by turning on the vitamin D receptor and clearing LCA from the body. One obstacle that must be overcome, however, is that high intake of vitamin D or drugs that mimic vitamin D can lead to dangerous levels of calcium in the blood.

Colon cancer expert Bert Vogelstein, an HHMI investigator at the Sidney Kimmel Comprehensive Cancer Center at The Johns Hopkins University, said, "these studies provide important new clues to the relationship between vitamin D, bile acids, and colorectal cancer, and they have significant implications for colorectal cancer prevention in the future."

Mangelsdorf, Evans and their colleagues studied the effects of the bile acid, LCA, which is produced as a by-product when intestinal bacteria digest

primary bile acids produced in the liver. Primary bile acids help the body digest dietary fats. The experiments showed that LCA activates the vitamin D receptor, which then activates additional genes that help detoxify LCA.

“There’s an abundance of epidemiologic data, as well as some scientific data, suggesting a correlation between high-fat diets, bile acids such as LCA, and colon cancer,” said Mangelsdorf. “But there has been no causal link, which has been one of the frustrating aspects of trying to understand the relationship between our Western-style high-fat diet and colon cancer.

Although it had been shown that vitamin D can prevent colon cancer in rats treated with LCA, and that humans with defective vitamin D signaling pathways have a higher incidence of colon cancer, it remained unclear how vitamin D actually prevents colon cancer. A reasonable theory, according to Mangelsdorf, was that vitamin D and LCA both triggered a biochemical pathway involved in detoxifying LCA. The best candidate was a pathway that involved the vitamin D receptor.

In one set of studies, the researchers showed that the vitamin D receptor strongly binds to LCA. But the researchers also needed to demonstrate that binding LCA actually activates a key gene, called *CYP3A*, which triggers the cell’s detoxification machinery. The scientists attached a “reporter” gene to *CYP3A* in human cells in culture, so they could detect whether the *CYP3A* gene was switched on when LCA attached to the vitamin D receptor.

“Other investigators had published data showing that vitamin D could switch on this gene, but it was a big surprise that LCA could do it also,” said Mangelsdorf. The scientists also performed experiments in mice, in which they found that feeding the animals LCA led to the activation of certain vitamin-D-receptor target genes.

The scientists ultimately demonstrated that the vitamin D receptor was the only receptor activated by LCA. “We showed that in our knockout mice, LCA still induces the expression of *CYP3A*, just like vitamin D does,” said Mangelsdorf. “So this crucial experiment demonstrated that vitamin D and LCA were not working through another receptor but through the vitamin D receptor.”

According to Mangelsdorf, the findings suggest that the vitamin D receptor acts as a sensor for the toxic chemical LCA. Other receptors in the body can sense dietary fats and other foreign chemicals, and serve to “alert” the body to begin detoxification when the chemicals reach dangerous levels.

“Our findings suggest a new look at the relationship between nutrition and cancer, particularly how vitamin D protects against colon cancer,” he said. “One problem with using vitamin D as a protective drug has always been that it produces hypercalcemia. But now we know that there’s another endogenous compound, LCA, that can also attach to the receptor, this suggests that we can develop protective drugs that don’t produce hypercalcemia, but do activate the detoxification pathway.”