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Study Links Colon Cancer to Diabetes Drug

While it has long been known that a diet laden with fat can increase the risk of some kinds of cancers, the biochemical pathways that produce this effect have remained a mystery. Ronald Evans, a Howard Hughes Medical Institute (HHMI) investigator at The Salk Institute for Biological Studies in La Jolla, California, has evidence that a protein receptor lurking within cells may be the molecular switch that allows dietary lipids, or fats, to do their dirty work.

Writing in the September 1998 issue of the journal *Nature Medicine*, Evans and his colleagues suggest that a protein known as peroxisome proliferator-activated receptor, or PPAR γ , may also be the switch that lets dietary fats to promote colorectal cancer, a disease that kills an estimated 510,000 people annually worldwide.

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— Enrique Saez

This study also raises concerns about the long-term safety of taking the diabetes drug troglitazone, which interacts with PPAR γ and, in essence, mimics some of the effects of a high-fat diet. By dosing mice predisposed to develop intestinal tumors with troglitazone, the HHMI team induced a significantly greater number of colon polyps.

In the study, troglitazone-activated PPAR γ caused more colon tumors to form. The discovery that PPAR γ can promote tumor formation in the colon provides the first evidence of the molecular basis of diet-related cancers. PPAR γ is believed to be a key regulator of fat breakdown and storage in the body.

"PPAR γ represents a potential molecular link between diet and increased risk of cancer," according to Enrique Saez, lead author of the study and a postdoctoral fellow at The Salk Institute. "But at this stage we can only speak to colon cancer," although he explains that the finding may have implications for the genesis of other diet-induced carcinomas such as breast and prostate cancer. Investigators from the University of California and the Veterans Administration Center, both in San Diego, and the University of Texas at Houston Medical School contributed to this work.

PPAR γ is one of a family of proteins found in the nucleus of cells that bind to certain chemicals, or ligands, and subsequently modulate γ include high levels of lipids and drugs such as troglitazone. "These receptors usually are inactive until a hormone or other ligand binds to them and stimulates activity," said Saez, whose work in Evans's laboratory focuses on the molecular genetics of disease.

Results of this study agree with those in another mouse study by a French team, also published in the September 1998 *Nature Medicine*. In contrast, a third study in the same journal, conducted in cultured human colon cancer cells by a team from the Dana-Farber Cancer Institute, suggests that PPAR γ could be used to help suppress the growth of colon cancer cells.

The apparent contradiction, according to Saez, may stem from the difference in models used to study PPAR γ . "When you do the experiment in an animal, things are very different. When you take cells out of that context, it's not comparable to what's going on in the colon. Cell culture studies cannot replicate the complex web of interactions that take place in the whole organism."

Saez also noted that the study is likely to have implications for the treatment of type II diabetes in humans. Although the study was conducted in mice, the molecular basis for colon cancer in humans and mice is similar. As a result, diabetics treated with troglitazone or similar drugs, and who have a family history of colorectal cancer, may be at increased risk, he said.

Saez adds, though, that the cancer-promoting effects of troglitazone in mice predisposed to colon cancer were not seen in normal mice. "We looked at normal mice and troglitazone didn't induce tumors. It is not carcinogenic, but it appears to cooperate with other genes to bring about tumor formation."

"It would be prudent," the authors write, "to evaluate the effects of troglitazone and other PPAR γ activators on the pathogenesis of human colorectal carcinoma." This sentiment is echoed in an editorial accompanying the three articles in *Nature Medicine*.

The drug troglitazone, sold under the tradename Rezulin, was launched in March 1997 as a new treatment for adult-onset or type II insulin-resistant diabetes. It has been widely prescribed in the United States, but the drug has since been associated with at least 26 deaths from liver failure.