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Synthetic triterpenoids show promise in preventing colitis-associated colon cancer

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Researchers from Case Western Reserve and Dartmouth universities have shown that a class of small antioxidant molecules carries enormous promise for supressing colon cancer associated with colitis. These findings, published in an early June edition of the *Journal of Clinical Investigation*, offer hope that physicians ultimately will be able to reduce dramatically the number of sufferers of this inflammatory bowel disease (IBD) who go on to develop colon cancer.

The molecules, known as synthetic triterpenoids, appear to achieve their positive effect in two ways. First, they impede inflammation, often a flashpoint that contributes to the development of colon cancer. Second, they increase 15-hydroxyprostaglandin dehydrogenase (15-PGDH), a gene product that is known at high levels to protect against colon cancer. The oral administration of synthetic triterpenoids showed such success in mice that the researchers believe that clinical trials could demonstrate their efficacy in chemoprevention—that is, the administration of medicine to stop or delay the onset of cancer, rather than treat it.

"Patients with inflammatory bowel disease have a 10-fold greater risk of colon cancer, placing it among the top three high-risk conditions for colorectal cancer," said senior author and hematologist/oncologist John Letterio, MD, professor of pediatrics, Case Western Reserve University School of Medicine, and director of the Angie Fowler Adolescent and Young Adult Cancer Institute, University Hospitals Rainbow Babies & Children's Hospital. "Common epithelial cancers develop over a period of years, even decades, in populations at high risk due to genetic

predisposition, so chemoprevention strategies could delay, or even halt, onset of clinically evident colon cancer."

Joining Letterio in this investigation was Michael B. Sporn, MD, professor of pharmacology and toxicology, Dartmouth Medical School, who first coined the term "chemoprevention" nearly four decades ago and has investigated synthesized triterpenoids since 1995, demonstrating their effectiveness against epithelial cancers. Sporn collaborates in scientific investigation with leading physicians throughout the country, and Letterio's collaboration with Sporn was a natural because the two worked together when Letterio was a post-doctoral fellow. Colleague Sanford Markowitz, MD, PhD, Ingalls Professor of Cancer Genetics at Case Western Reserve School of Medicine, served an important role in this investigation because of his expertise as the innovator who first characterized 15-PGDH, an important tumor suppressor and natural anti-inflammatory.

"We have been intrigued by recent findings that inflammatory cytokines, such as TNF-alpha, hinder the expression of 15-PGDH," Letterio said. "We found that triterpenoids could reverse the inflammatory process by allowing 15-PGDH expression to resume. Triterpenoids also impede expression of the cyclooxygenase-2 (COX-2), an enzyme known to fuel inflammation. Between reversing the effects of TNF-alpha and of COX-2, this class of small molecules might suppress colitis-associated colon cancer."

In mice genetically engineered toward proneness for inflammation-driven intestinal neoplasia, oral administered triterpenoids increased the survival of the mice. Triterpenoid molecules also suppressed intestinal epithelial neoplasia by decreasing production of inflammatory mediators and increasing expression of colon-cancer-suppressing 15-PGDH.

Investigators also found that triterpenoids administered to normal mice

prevented their development of inflammation and colon cancer, despite their exposure to carcinogens known to cause these two conditions. In addition, they discovered that triterpenoids trigger epithelial cells' responses to TGF-beta, a signaling pathway known to activate 15-PGDH.

"Two observations are particularly significant in this study," Letterio said. "First, our studies in mice demonstrate a cancer chemoprevention effect with triterpenoids. Second, our data also show that the production of 15-PGDH in mice depended on the presence of an intact TGF-beta signalling pathway. This pathway ensures that internal conditions remain relatively constant in intestinal mucosa, both in the regulation of epithelial cell differentiation and development of inducible regulatory T cells to fend off cancer."

The research team next will focus on assessing the effect of triterpenoids for models of IBD and colon cancer that are not related to colitis. Investigators also want to explore whether plant-derived natural triterpenoids with similar properties to laboratory-produced synthetic triterpenoids might offer a comparable benefit.

"The argument is strong for pursuing human trials in cancer chemoprevention with triterpenoids," Letterio said. "There are many questions about safety, efficacy, intermittent vs. continuous administration, and synthetic vs. natural triterpenoid. Carefully designed clinical trials and a collaborative approach between industry and academics will be needed to address these questions."

Markowitz concurs and additionally addresses the significance of findings in this latest investigation.

"Colon cancer is among the most feared consequences of long-term ulcerative colitis," he said. "Even with intense surveillance of the colon

by colonoscopy and random biopsies, development of cancer is not always caught in time. The finding that synthetic triterpenoids can prevent colon cancer in the mouse model is the first true advance in this field and opens up a novel opportunity for developing new drugs for use in human patients."

Provided by Case Western Reserve University

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