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# Researchers make discovery in colon cancer prevention

May 18 2009

A new study finds that individuals who have low expression of the "Celebrex gene," 15-PGDH, are actually resistant to Celebrex treatment when used to prevent colon cancer. The study, published in this week's issue of the *Proceedings of the National Academy of Sciences* (PNAS), is by Sanford Markowitz, M.D., Ph.D., the Markowitz-Ingalls Professor of Cancer Genetics at the Case Western Reserve University School of Medicine and an oncologist at the Ireland Cancer Center of University Hospitals Case Medical Center and his colleagues.

"These findings have two important practical implications," said Markowitz, who is also an investigator in the Howard Hughes Medical Institute. "First, they suggest that measurement of 15-PGDH may identify which individuals are most likely to benefit from treatment with Celecoxib as a colon tumor preventative. Second, they suggest that identifying drugs that could increase 15-PGDH expression in the colon could be a potent new strategy for preventing development of tumors in the colon."

In the Adenoma Prevention with Celecoxib (APC) trial, a clinical trial conducted by Monica Bertagnolli, M.D. at the Harvard Brigham and Women's Hospital and designed to test Celecoxib for the prevention of sporadic colorectal adenomas, the researchers showed that Celecoxib (brand name Celebrex, a Cox-2 inhibitor that relieves pain and inflammation without harming the digestive tract) treatment of individuals who had previously developed colon adenomas cut the rate of developing new adenomas by one-third, and cut the rate of developing

new large adenomas by two-thirds. Some individuals however proved resistant to Celecoxib treatment and developed new colon tumors even while on the drug. Colon adenomatous polyps are benign tumors that are the immediate precursors of colon cancers.

Previous studies by Markowitz published in PNAS (December 2004 and July 2006) discovered that the gene 15-PGDH is expressed by the normal colon and acts similarly to Celecoxib in preventing colon tumors by inhibiting the COX-2 pathway.

The current study leads the researchers to ask, 'could protection from colon tumors by Celecoxib actually require the joint action of both the drug and the 15-PGDH gene?'

To answer the question the investigators examined mice that genetically lacked the gene 15-PGDH. In these mice, Celecoxib proved unable to prevent the development of colon tumors, suggesting that both the drug and the gene are needed to protect the colon from tumor development.

The investigators then examined colon biopsies from human patients who had participated in the APC trial of Celecoxib. They found that among these individuals colon 15-PGDH levels varied by 12-fold from lowest to highest. Most importantly, they found that the patients who were resistant to Celecoxib and had developed new colon tumors were all individuals who had low levels of colonic 15-PGDH. Thus in both mice and humans, Celecoxib works to prevent colon tumors only if levels of colonic 15-PGDH are high, while low levels of 15-PGDH leads to Celecoxib resistance.

Markowitz and Bertagnolli point out that these findings should be further confirmed in additional studies with larger numbers of patients. They also agree that it will be important to determine if differences in 15-PGDH levels also account for differences between different individuals

in the effectiveness of Celecoxib and similar type drugs, when used for treating pain or inflammation.

Source: Case Western Reserve University (news : web)