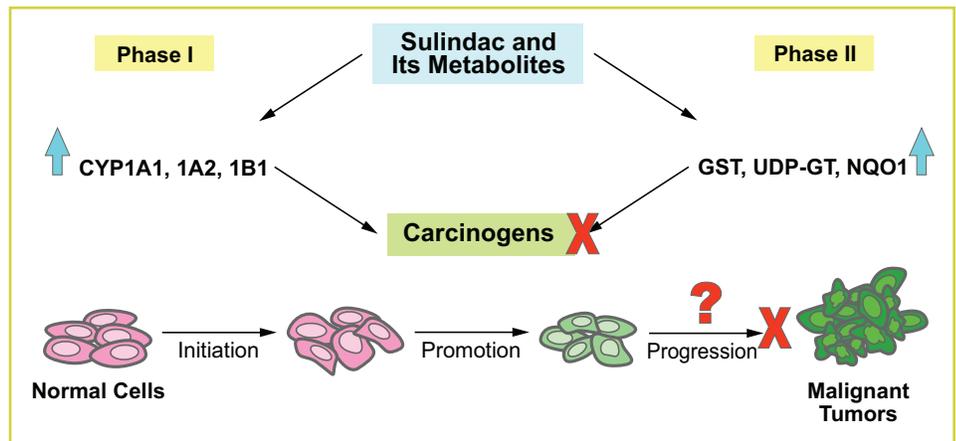


NSAIDs: Aiding the Fight Against Cancer

Colorectal cancer claims more than 50,000 lives each year in the United States alone. There is increasing evidence that nonsteroidal anti-inflammatory drugs (NSAIDs) may reduce the risk of colorectal and other cancers, but scientists have not been able to explain how or why. Researchers at the National Cancer Institute have begun to unlock this mystery.

When a xenobiotic—a chemical not expected to be present in an organism—is introduced, enzymes protect the organism by metabolizing or detoxifying the molecule. Enzymes in the colon, such as CYPs and phase 2 enzymes, help defend the body from polycyclic aromatic hydrocarbons (PAHs), xenobiotics thought to cause some cancers. A recent study found that the NSAID sulindac, which has been shown to reduce the size and number of precancerous colorectal polyps, increases the expression of those enzymes, suggesting a mechanism by which it may help prevent PAH-induced cancers.

Grace Chao Yeh, Ph.D., of the Laboratory of Metabolism at NCI-Frederick, and members of her lab teamed up with Henry Ciolino, Ph.D., from the University of Texas at Austin, to test the influence of sulindac and its metabolites, sulindac sulfide and sulindac sulfone, on two human colon cancer



Yeh and colleagues found that the NSAID sulindac and its metabolites increase the expression of genes for several phase 1 and phase 2 detoxifying enzymes, suggesting a mechanism by which this agent may help prevent carcinogen-induced cancers.

cell lines. Sulindac and sulindac sulfide generated a significant increase in CYP enzyme activity, particularly CYP1A1, CYP1A2, and CYP1B1, three enzymes active in xenobiotic metabolism. Interestingly, the increase was sustained at maximal levels for six days after a single treatment.

Dr. Yeh and colleagues hypothesized that sulindac and its metabolites increased CYP enzyme activity by increasing CYP levels in the cell. As suspected, they found that sulindac and sulindac sulfide increased mRNA levels for CYP1A1, CYP1A2, and CYP1B1. Experiments on CYP1A1 revealed that this increase was due to higher levels of CYP gene transcription, the first step in translating the genetic code into a functional protein. This boost in gene expression corresponded to

increased binding of activated aryl hydrocarbon receptor—a protein that activates CYP transcription—to the region of DNA that controls expression of CYP1A1, indicating a possible mechanism of sulindac-activated CYP1A1 gene expression.

Sulindac and both of its metabolites also influenced phase 2 enzymes that help protect against xenobiotics. Expression of the genes that code for UDP-GT, NQO1, and GST-pi increased. All of these proteins chemically modify xenobiotics to reduce their toxicity or facilitate their excretion from the cell. NQO1 enzymatic activity increased as well.

These findings, published in a recent edition of the *International Journal of Cancer* and co-lead authored by

NCI-Frederick's Sara Bass, M.S. (Laboratory of Metabolism), could explain how sulindac and its metabolites defend against PAH-induced cancers and may be the first demonstration of an effect on both CYP and phase 2 enzymes by an NSAID. Because

NSAIDs have also been linked to a reduced incidence of several other cancers, including breast, stomach, prostate, and lung cancers, this new explanation could lead to preventive interventions that would affect many thousands of people in years to come.

References

American Cancer Society. *Cancer Facts & Figures 2007*.

Ciolino HP, Bass SE, MacDonald CJ, Cheng RY, Yeh GC. Sulindac and its metabolites induce carcinogen metabolizing enzymes in human colon cancer cells. *Int J Cancer* 122: 990–8, 2008.